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TITLE: A Randomized Phase 2 Trial of 177Lu Radiolabeled Anti-PSMA Monoclonal Antibody J591 in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer

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14. ABSTRACT

Clinical trial has received WCMC IRB and CTSC approval with enrollment of initial 3 subjects at WCMC. An additional 12 subjects enrolled (7 treated) at participating sub-sites. Reports submitted to WCMC DSMB with recommendation to proceed with enrollment.

15. SUBJECT TERMS
Prostate cancer, PSA, PSMA, monoclonal antibody, radioimmunotherapy

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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I. Introduction

Men with biochemically progressive (PSA only) prostate cancer have non-radiographically apparent micrometastases that may be targeted with radioimmunotherapy. Prostate specific membrane antigen (PSMA) is the single, most well-established, highly restricted prostate epithelial cell membrane antigen known and is expressed by virtually all prostate cancers. Investigators at WCMC have generated a high-affinity antibody (J591) against the external portion of PSMA that binds to viable PSMA-expressing cells and is internalized. Studies utilizing J591 radiolabeled with Lutetium-177 (^{177}Lu) have demonstrated safety, efficacy, and accurate, selective tumor targeting in the metastatic castration-resistant prostate cancer (CRPC) setting. The physical properties of ^{177}Lu are best suited for 1-3 mm tumors (those not seen on standard imaging modalities). The hypothesis is that the addition of ^{177}Lu-J591 to ketoconazole will improve time to radiographically apparent metastases in men with biochemically progressive non-metastatic CRPC.

In this multi-center, double-blind, randomized phase II trial involving men with relapsed prostate cancer and biochemical only (PSA) progression (no radiographic evidence of metastases) despite castration at high risk of early development of metastases. The primary endpoint will be to compare the percentage of men with metastases at 18 months receiving ketoconazole plus ^{177}Lu-J591 vs ketoconazole plus trace-labeled ^{111}In-J591 (i.e. placebo). Secondary endpoints include PSA response, toxicity, progression-free survival, overall survival, the ability of radiolabeled J591 to image otherwise non-radiographically apparent metastatic sites, the prognostic and predictive capability of circulating tumor cells, baseline adrenal androgen levels, and circulating markers of hemostatic activation, fibrinolysis, and angiogenesis. With a sample size of 127 (2:1 randomization), the study will have a ≥ 0.80 power with a pre-set alpha of 5% to determine an absolute difference in 18-month metastasis free survival. An interim analysis after 12 months of follow-up will be performed and reviewed by the external DSMB (necessitating increase in sample size by 10% to 140). Stopping limits will be imposed such that a significant observed difference in the metastasis-free proportion will be grounds for the consideration of early termination of the study using an adjusted significance level corresponding to the O'Brien-Fleming group sequential rule.

II. Body

Overview:

- 3 subjects have been enrolled and treated at Weill Cornell Medical College with two additional screen failures and at least 20 pre-screen failures.
- 8 subjects have been enrolled and 6 treated to date at Indiana University with additional pre-screen and screen failures
- 1 subject has been enrolled at University of Iowa but screen failed
- 3 subjects have been enrolled with 1 treated to date at University of Southern California with at least 2 additional pre-screen failures.

SOW Task **1a**, **1b**: Additional sites are in various stages of regulatory approval:

IRB Approved and site activated:
- Weill Cornell Medical College (IRB Approved 09Jan2009)
- University of Iowa (IRB Approved 24Jun2010)
- Indiana University (IRB Approved 29Jun2010)
- University of Southern California (IRB Approved 10Jan2011)

IRB Approval in progress:
- Emory University –IRB approved; contract approval pending
- Nevada Cancer Institute – scientific review approved, IRB and contract approval pending
- Jefferson Kimmel Cancer Center Thomas Jefferson University – scientific review/IRB review in progress
- University of Utah – in scientific review
- University of Medicine and Dentistry, New Jersey – in scientific review

Anticipated to initiate IRB start-up:
- University of Pittsburgh Medical Center
- Washington University
- Cedars Sinai Medical Center
- University of Washington
- Karmanos Cancer Institute, Wayne State University
- Baylor College of Medicine / Houston VAMC

The study is currently being primarily offered via the CTSA and PCCTC groups (see "Problem Areas" below)

Task **1c**: Amendments have been approved by ORP and WCMC IRB

SOW Task **2a**: See 1a/b above
Task **2b**: Currently completing safety lead-in phase
Task **2c**: Weekly email communication with sites, phone/teleconferences when necessary; monthly teleconferences to begin July, 2011
Task **2d**: Ongoing IRB and FDA updates; last DSMB submission May, 2011

III. Key Research Accomplishments

- The protocol has been approved by the WCMC IRB and CTSC as well as ORP
- The study was presented as a poster presentation at the 2011 annual scientific meeting of the American Society of Clinical Oncologists (abstract and poster attached)
- The DOD-sponsored PCCTC has agreed to support the study
- Successful fundraising to increase clinical trial budget

IV. Reportable Outcomes

Abstract: S.T. Tagawa, N. Hahn, D. Vaena, D. Quinn, P. Christos, J. Osborne, S. Vallabhajosula, G. Mileo, K. Nadeau, L. Tyrell, A. Saran, H. Beltran, S.J. Goldsmith, D. M. Nanus. Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for non-metastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial. J Clin Oncol 29: 2011 (suppl; Abstr TPS193)

Presentation: Poster presentation, 2011 ASCO Annual Meeting

V. Conclusions

Biochemical relapse is common after local therapy for prostate cancer. Based on the physical properties of ^{177}Lu and the disease targeting ability of J591, ^{177}Lu-J591 is ideally suited to make a significant impact on this state of disease. The protocol has been approved and activated at the initial sites and progress continues at additional sites.

VI. References

None used

VII. Appendices

Attachment 1: Tagawa et al. abstract, J Clin Oncol 29: 2011 (suppl; Abstr TPS248)

Attachment 2: Poster presentation

Attachment 3: Approval documents: (a) Most recent WCMC IRB approval documents (b) DSMB full board review outcome letter

Attachment 4: Letter of support from PCCTC

Attachment 5: Financial support letter

ASCO American Society of Clinical Oncology
www.asco.org

Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial.

Sub-category:
Prostate Cancer

Category:
Genitourinary Cancer

Meeting:
2011 ASCO Annual Meeting

Session Type and Session Title:
Trials in Progress Poster Session, Trials in Progress Poster Session

Abstract No:
TPS193

Citation:
J Clin Oncol 29: 2011 (suppl; abstr TPS193)

Author(s):
S. T. Tagawa, N. M. Hahn, D. A. Vaena, D. I. Quinn, W. K. Kelly, P. J. Christos, J. Osborne, S. Vallabhajosula, K. Nadeau, G. Mileo, L. Tyrell, A. Saran, C. Ecker, H. Beltran, S. J. Goldsmith, D. M. Nanus; Weill Cornell Medical College, New York, NY; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; University of Iowa, Iowa City, IA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Thomas Jefferson University Hospital, Philadelphia, PA

Abstract Disclosures

Abstract:

Background: Biochemical recurrence without evidence of PC on standard CT/MRI and bone scans after local therapy is common. Salvage radiotherapy affords a cure to select patients (pts) with PSA relapse, but most progress because of micrometastatic PC outside of the radiation field. J591 is a monoclonal antibody that targets the extracellular domain of PSMA. A phase II trial of single-dose ^{177}Lu-J591 radioimmunotherapy (RIT) in pts with progressive, metastatic (met) CRPC demonstrated excellent targeting of met sites, efficacy, and acceptable toxicity [Tagawa et al, ASCO 2008]. RIT appears to have its greatest impact in the setting of minimal disease [Kaminski, NEJM 2005; Leonard, JCO2005; Press, JCO 2006] and the beta emission of ^{177}Lu is best suited for lesions 1-3 mm in diameter [O'Donoghue, J Nuc Med 1995] (i.e. micrometastatic disease). **Methods:** In this multicenter DOD-sponsored study, men with high-risk CRPC (PSA doubling time < 8 months and/or PSA > 20 [Smith, JCO 2005]) and no evidence of disease on CT/MRI and bone scans are randomized 2:1 to receive double-blinded ^{177}Lu-J951 vs ^{111}In-J591 (control) and undergo planar gamma camera imaging with SPECT following infusion. All pts receive ketoconazole plus hydrocortisone. The primary endpoint of the study is 18-month met-free survival. 140 pts will be treated to allow 80% power with a 2-sided alpha of 5% to detect a 25% absolute difference (50% vs 75% met-free) in radiographically apparent mets at 18 months (with interim analysis after 50% of pts have at least 12 months follow up). Secondary/exploratory endpoints include evaluation of radiolabeled J591 imaging to detect sites of mets not apparent on standard CT/MRI and bone scan, validation of adrenal androgen levels as biomarkers for ketoconazole [Ryan Clin Cancer Res 2007], analysis of circulating tumor cells captured via CellSearch methodology as well as PSMA-GEDI capture [Gleghorn, Lab Chip 2010] for PSMA expression and counts to predict the appearance of radiographic metastases, and exploration of hemostatic/fibrinolytic/angiogenic plasma biomarkers.

Associated Presentation(s):

1. Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial.

Meeting: 2011 ASCO Annual Meeting

Presenter: Scott T. Tagawa
Session: Trials in Progress Poster Session (Trials in Progress Poster Session)

Other Abstracts in this Sub-Category:

1. SYNERGY: A randomized phase III study comparing first-line docetaxel/prednisone to docetaxel/prednisone plus custirsen in metastatic castrate-resistant prostate cancer (mCRPC).

Meeting: 2011 ASCO Annual Meeting Abstract No: TPS180 First Author: K. N. Chi
Category: Genitourinary Cancer - Prostate Cancer

2. A randomized, double-blind, phase III trial comparing ipilimumab versus placebo following radiotherapy (RT) in patients (pts) with castration-resistant prostate cancer (CRPC) who have received prior treatment with docetaxel (D).

Meeting: 2011 ASCO Annual Meeting Abstract No: TPS181 First Author: C. G. Drake
Category: Genitourinary Cancer - Prostate Cancer

3. Randomized, double-blind, phase III trial to compare the efficacy of ipilimumab (Ipi) versus placebo in asymptomatic or minimally symptomatic patients (pts) with metastatic chemotherapy-naïve castration-resistant prostate cancer (CRPC).

Meeting: 2011 ASCO Annual Meeting Abstract No: TPS182 First Author: T. M. Beer
Category: Genitourinary Cancer - Prostate Cancer

More...

Abstracts by S. T. Tagawa:

1. Clinical outcome of single agent volasertib (BI 6727) as second-line treatment of patients (pts) with advanced or metastatic urothelial cancer (UC).

Meeting: 2011 ASCO Annual Meeting Abstract No: 4567 First Author: W. M. Stadler
Category: Genitourinary Cancer - Other GU Cancer

2. Final phase II results of NCI 6981: A phase I/II study of sorafenib (S) plus gemcitabine (GEM) and capecitabine (CAP) for advanced renal cell carcinoma (RCC).

Meeting: 2011 ASCO Annual Meeting Abstract No: e15165 First Author: S. T. Tagawa
Category: Genitourinary Cancer - Kidney Cancer

3. Molecular characterization of neuroendocrine prostate cancer (NEPC) and identification of new drug targets.

Meeting: 2011 ASCO Annual Meeting Abstract No: 4536 First Author: H. Beltran
Category: Genitourinary Cancer - Prostate Cancer

More...

Presentations by S. T. Tagawa:

1. Radiolabeled anti-prostate specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) for nonmetastatic castration-resistant prostate cancer (CRPC): A randomized phase II trial.

Meeting: 2011 ASCO Annual Meeting
Presenter: Scott T. Tagawa, MD, MS
Session: Trials in Progress Poster Session (Trials in Progress Poster Session)

2. A randomized phase II trial of ^{177}lu radiolabeled monoclonal antibody J591 (^{177}Lu-J591) and ketoconazole in patients (pts) with high-risk castrate biochemically relapsed prostate cancer (PC) after local therapy.

Meeting: 2010 ASCO Annual Meeting

Presenter: Scott T. Tagawa
Session: Trials in Progress Poster Session (Trials in Progress Poster Session)

3. Phase I trial of fractionated-dose ^{177}lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (^{177}Lu-J591) in patients (pts) with metastatic castration-resistant prostate cancer (metCRPC).

Meeting: 2010 ASCO Annual Meeting
Presenter: Scott T. Tagawa
Session: Genitourinary Cancer (General Poster Session)

More...

▸ ***Educational Book Manuscripts by S. T. Tagawa*:**

No items found.

RADIOLABELED ANTI-PROSTATE SPECIFIC MEMBRANE ANTIGEN (PSMA) MONOCLONAL ANTIBODY J591 (^{177}Lu-J591) FOR NON-METASTATIC CASTRATION-RESISTANT PROSTAT CANCER (CRPC): A RANDOMIZED PHASE II TRIAL

Scott T. Tagawa, Noah Hahn, Daniel Vaena, David Quinn, Mark Stein, Joseph Osborne, Paul J. Christos,
Shankar Vallabhajosula, Gina Mileo, Koty Nadeau, Lauren Tyrell, Ankeeta Saran, Himisha Beltran, Stanley J. Goldsmith, David M. Nanus
Weill Cornell Medical College, Indiana University, University of Iowa, University of Southern California, University of Medicine and Dentistry New Jersey

BACKGROUND

Radiolabeled J591

- J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extracellular domain of viable PSMA+ cells with rapid internalization
  Liu et al, Cancer Res 1997; Liu et al. Cancer Res 1998
- Phase I trials of radiolabeled J591 demonstrated safety, sensitive and specific tumor targeting, and preliminary evidence of activity
  Milowsky et al, JCO 2004, Bander et al, JCO 2005
- The MTD of ^{177}Lu-J591 was 70 mCi/m^2, with reversible myelosuppression

Phase II single-dose ^{177}Lu-J591 Radioimmunotherapy (RIT) for metCRPC

- Two successive cohorts of pts with progressive metCRPC received one dose of ^{177}Lu -J591: Cohort 1 (65mCi/m^2), 15 pts; Cohort 2: (70mCi/m^2, phase I MTD), 17 pts. The 1° endpoint was PSA and/or measurable disease response with 2° endpoint of toxicity. A ^{177}Lu-J591 imaging study was performed to confirm tumor targeting.
- Median age was 71 (range 51-88), median baseline PSA 81.6 (3.3 – 2184.6). 3 with ECOG PS 0, 27 PS 1, 2 PS 2; 97% had bone mets, 25% extra-osseous visceral mets (2 liver, 5 lung, 1 adrenal). The majority (18 pts, 56%) progressed on at least docetaxel.
- Overall, 3 (10%) experienced ≥ 50% PSA decline and 10 (31%) experienced ≥30% PSA decline. Those with PSA decline lived longer (p=0.01). Targeting of known sites of PC metastases was seen in 30 of 32 (94%) pts [Fig 1]. More pts treated at the phase I MTD (70 mCi/m^2) experienced PSA declines (71%) than those treated with 65mCi/m^2 (46%), p=0.06 [Fig 2].
- 9 pts received 1-4 platelet transfusions (median 2); no significant hemorrhagic complications occurred. Of 32 evaluable pts, 27 had return to normal platelet counts and 4 recovered to near-normal. 27% experienced transient Gr 4 neutropenia without fevers No serious attributable non-heme toxicity occurred.

Current/Future aims in metastatic CRPC

To develop biomarkers to optimally select pts (imaging may predict response, exploration of PSMA expression in CTC's), improve therapeutic profile with dose fractionation [Tagawa et al, ASCO 2010], and combine with chemo, utilizing improved tolerability of fractionated dose RIT + the radiosensitizing and debulking properties of docetaxel [Beltran et al; ASCO 2010].

The optimal setting for anti-PSMA RIT, especially based upon the physical properties of ^{177}Lu, may be micro-metastatic disease.

Supported by:
Department of Defense PC081664 (W81XWH-09-1-0596)
Prostate Cancer Foundation
NIH 1-KL2-RR024997-01; PTBF5405; ULI RR024996 (WCMC CTSC)

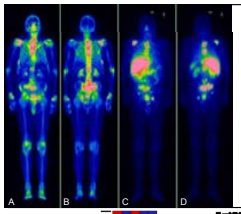


Figure 1

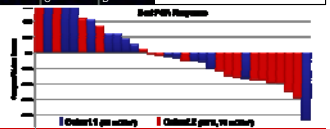
Left: ^{99m}Tc-MDP bone scan
Ant (A) and post (B) images of pre-treatment bony metastases

Right: ^{177}Lu-J591 scan
Ant (C) and post (D) total body images obtained via dual head gamma camera of sites of uptake 7 days after ^{177}Lu-J591 administration

(NOTE: J591 is cpartially leared via liver resulting in non-specific uptake)

Figure 2

Waterfall Plot of best PSA response



β Emitting Radionuclides: Rationale for ^{177}Lu-J591

		^{131}I	^{90}Y	^{177}Lu
Physical Half Life (days)		8.05	2.67	6.7
Beta Particles (mEv)	Maximum	0.61	2.280	0.497
	Average	0.20	0.935	0.149
Range in Tissue (mm)	Maximum	2.4	12.0	2.20
	Average	0.4	2.7	0.25
Gamma Emission (mEv)		0.364 (81%)	none	0.113 -0.208 (7-11%)

^{177}Lutetium: [O'Donoghue et al, J Nuc Med 2005]

- Low energy particle with short range
- Allow higher doses with less marrow toxicity
- Gamma emission allows imaging
- May be suboptimal for bulky tumors
  (i.e. suboptimal for disease state tested to date: metastatic CRPC)
- Physical properties more optimal for curability in small tumors (1-3 mm)

Radiolabeled (RL) J591 Efficacy

Over a decade of clinical experience
[Akhtar et al, ASCO GU 2011: 3 Ph I, 1 Ph 2 trials in 137 pts]

PSA declines: Majority (54%) with PSA declines

- More PSA declines at MTD doses (p<0.001 for ≥ 30% decline, p=0.05 for any)

Objective Radiographic Responses: (36.4% had measurable disease)

- More radiographic responses with ^{90}Y-J591 than ^{177}Lu-J591 (p=0.04)
- All pts with radiographic response also had significant PSA declines

CTC Counts: 84% became or remained favorable after RL-J591(n=19)

Survival: Overall Survival 16.6 mo [95% CI 13.4, 19.7]

- PSA decline associated with survival (22.1 vs 12.1 mo, p=0.001)

Salvage Anti-PSMA Radioimmunotherapy

- Biochemical only relapse is common, affecting approximately 50,000 new men per year in the U.S. alone
- PC is radiosensitive; salvage radiotherapy is an effective salvage therapy for selected pts, but most eventually suffer distant relapse/progression because of micrometastatic disease outside of the RT field [Ward J Urol 2004; Freedland J Urol 2007; Pazona J Urol 2005; Buskirk J Urol 2006; Stephenson JAMA 2004, JCO 2007]

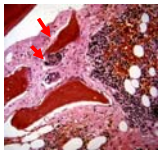


Figure 3

Sites of prostate cancer metastases (arrows) in bone marrow. These tumor deposits are too small to be detected on standard imaging and are not amenable to standard salvage therapy (external beam RT, surgery, cryotherapy, etc.)

- Radioimmunotherapy may have greatest effect in setting of minimal disease [Kaminski Blood 2002, JCO 2005, NEJM 2005; Press Blood 2003, JCO 2006; Leonard JCO 2005]
- Nearly all prostate cancer cells express PSMA [Israeli Cancer Res 1994; Silver Clin Cancer Res 1997; Bostwick Cancer 1998; Wright Urol Oncol 1995; Wright Urology 1996]
- J591 targets known sites of disease with efficacy in the advanced setting
- ^{177}Lu is optimal for 1-3 mm lesions, i.e. micrometastatic (small volume) disease not apparent on standard scans [O'Donoghue et al, J Nuc Med 2005]
- "Targeted radiotherapy" with ^{177}Lu-J591 may be able to eliminate sites of micrometastatic disease in the biochemically relapsed setting

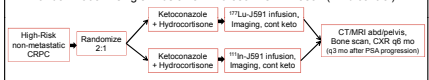
RANDOMIZED Ph II: Lu-J591 in NONMETASTATIC CRPC

ENTRY CRITERIA (summary)

- Biochemical relapse after primary local therapy
- High risk castrate-resistant PSA progression
  - rising PSA despite medical/surgical castration and testosterone < 50 ng/mL
  - absolute PSA > 20 and/or PSA DT < 8 mo
  [Smith et al, J Clin Oncol 2005]
- CT/MRI and bone scan without evidence of metastatic disease
- Intact hematologic and organ function
- ECOG Performance Status ≤ 2

TREATMENT

- All pts: ketoconazole 400 mg TID + hydrocortisone 20 AM, 10 PM
- 2:1 randomization: single infusion of ^{177}Lu-J591 vs ^{111}In-J591 (mAb control)



- 1° endpoint: metastasis-free survival at 18 months
  Based upon entry criteria, 50% expected to have mets at 18 months. With a sample size of 127 (2:1 randomization), ≥ 0.80 power with alpha of 5% to determine difference in 18-month metastasis free survival (75% vs 50%). Interim analysis after 50% of 18-month MFS events required for final analysis with futility analysis performed (increasing sample size to 140)
- 2° endpoints: ability of radiolabeled J591 to image micrometastatic disease, circulating tumor cell enumeration and PSMA expression, PFS, adrenal hormone levels, markers of hemostatic activation, fibrinolysis, angiogenesis

SUMMARY

Based upon the recurrence pattern of prostate cancer, its known radiosensitivity, J591's known ability to target sites of metastatic disease, and the physical properties of ^{177}Lu, anti-PSMA-based salvage RIT has the possibility of significantly impacting the natural course of relapsed prostate cancer

STATUS:

- The study is open at 4 centers and the initial subjects are accruing
- The study will open at additional sites throughout the United States, including sites in the CTSA consortium and Prostate Cancer Clinical Trials Consortium

Clinicaltrials.gov NCT00859781

Weill Cornell Medical College

Rosemary Kraemer, Ph.D.
Director, Human Research Protections Programs
Division of Research Integrity
Research and Sponsored Programs
407 East 61st Street, RR-110
New York, New York 10065

Telephone: 646-962-8200
Fax: 646-962-0533
Email: rtkraeme@med.cornell.edu

Date: January 12, 2011

To: Scott Tagawa, MD

From: Rosemary Kraemer, Ph.D.

Re: Continuing Review - Protocol # **0810010067**
- Revised Informed Consent Form dated May 25, 2010
- HIPAA Authorization (Research Privacy Form 1)

Amendment: Removal of co-investigator: Jodi Selzer

Your response to issues raised during continuing review of the protocol entitled, "**A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy**" was reviewed at the **January 10, 2011** meeting of Institutional Review Board (IRB # 2) and was approved for a period of 12 months expiring **January 9, 2012**.

Please note subject recruitment, enrollment, study intervention, and data analysis has been approved at the WCMC site. However, the shipment of the radiopharmaceutical to the subsites cannot occur until there is a material transfer agreement between WCMC and each subsite in place. In addition, the Iowa approval letter must be revised to list Dr. Tagawa as the holder of the IND.

This approval is contingent upon continued adherence with institutional billing compliance policies and may be revoked at any time.

Investigators must notify the IRB in writing immediately, within 7 calendar days, of all adverse events, incidents, or information which are unexpected *and* related (or probably related) to participation in the research. This includes both serious and non-serious adverse events occurring to NYPH-WCMC subjects or others, as well as unexpected, study-related incidents and information. Unexpected, study-related incidents and information include, but are not limited to, protocol deviations, breaches of confidentiality, laboratory accidents, and new findings from animal research that suggest risk for human research subjects. *If the unexpected and related (or probably related) adverse event is the death of a research subject, then you must report it to the IRB within 24 hours of investigator notification.*

In addition, the reporting requirements of different regulatory bodies may differ both with regard to what must be reported and the required timing of reports. You must acquaint yourself with, and abide by, all federal and state regulatory reporting requirements applicable to this study. Please note that, in order to effectively monitor the safety of human research subjects, the IRB cannot accept adverse events that do not meet the criteria of unexpected and related (or possibly related) to participation in the research.

If your investigation undergoes a change in design or if unanticipated hazardous conditions emerge affecting the rights or welfare of the human subjects involved, you must submit an amendment to your protocol to the Institutional Review Board (and the Translational Research Advisory Committee [TRAC], if the Clinical and Translational Science Center [CTSC] is used). It will be your responsibility to request such review prior to initiation of any change in the study design of your project. Potential HHS and legal penalties for not doing so are severe. In addition, a new consent must be obtained from the subject after he or she is made aware of the changed conditions.

If your research study involves human tissues:
IRB approval is required in order to conduct research involving human subjects or their tissues. However, IRB approval to conduct a study does not supersede hospital policy which must be adhered to. If your protocol involves the use of tissue specimens, please familiarize yourself with Section 4.4 of the hospital By-Laws: "Specimens Removed During Resective Surgery" which states that all specimens removed during surgical diagnostic procedures shall be sent to Pathology Service.

To obtain tissue, you must submit a copy of this approval letter along with a copy of the Tissue Section C of the protocol (with proper initials) to the Pathology Administrative office in C-302. No tissue may be obtained or released until this paperwork is on file in the Department of Pathology and Laboratory Medicine.

If your research study involves obtaining consent:
Keep signed consent forms (IRB approved stamped forms must be used) permanently in the subject's hospital chart as a matter of record that the required disclosure was made. If the subject has no New York Presbyterian Hospital chart, you are responsible for retaining such signed forms in your personal research files.

Thank you for your cooperation and best wishes for a productive and rewarding research project.

The International Committee of Medical Journal Editors (ICMJE) has established a requirement that all clinical trials be entered in a public registry before the onset of patient enrollment as a condition of consideration for publication. Additional information may be found at http://clinicaltrials.gov/ and at http://www.icmje.org/clin_trialup.htm

Please contact the Protocol Registration System ("PRS") administrator by e-mail at ICR@med.cornell.edu to set up a PRS user account to register new and ongoing clinical trials. The e-mail should contain the PI's full name, department, phone number and e-mail address.

Weill Cornell Medical College

Data Safety Monitoring Board
407 East 61st Street, RR-110
New York, New York 10065

Telephone: 646-962-8192
E-mail: dsmb@med.cornell.edu
www.med.cornell.edu/research/rea_com/dsmb.html

Date: January 28, 2011

To: Scott Tagawa, MD.

From: Marcus Reidenberg, M.D.
DSMB Chairman

Re: DSMB Full Board Review
Protocol: #0810010067
Title: A Randomized Phase 2 Trial of 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy

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The Weill Cornell Medical College Data Safety Monitoring Board met on January 18, 2011 and reviewed the August 2010 periodic report for the above named protocol. The Board concurred with the Chair and primary reviewer's earlier assessment made via email in December 2010.

The DSMB recommends that the trial continue without modification. As a reminder, please be aware that according to your protocol:

- The PI must provide the DSMB with a narrative report of each patient who gets Grade 4 thrombocytopenia *within 2 weeks* of conclusion of episode, including duration, if bleeding occurred, and the outcome of the thrombocytopenia.

The protocol's next DSMB periodic review will occur on **March 8, 2011** according to its 6 month review schedule. Please send your periodic review submit2dsmb@med.cornell.edu via the website http://transfer.med.cornell.edu by **Tuesday, February 15, 2011**. An emailed reminder will be sent to you prior to the due date.

If you have any questions, please contact us by emailing dsmb@med.cornell.edu or calling the DSMB Coordinator, Lauren Odynocki, at (646) 962-8192.

Thank you.

Weill Cornell Medical College

Data Safety Monitoring Board
407 East 61st Street, RR-110
New York, New York 10065

Telephone: 646-962-8192
E-mail: dsmb@med.cornell.edu
www.med.cornell.edu/research/rea_com/dsmb.html

Date: June 17, 2011

To: Scott Tagawa, M.D. – IND Sponsor

From: Marcus Reidenberg, M.D.
DSMB Chairman

Re: DSMB Full Board Review

Protocol: #0304006100
Title: Phase II Trial of ^{177}Lutetium Radiolabeled Monoclonal Antibody Hu-J591-GS (^{177}Lu-J591) in Patients with Metastatic Androgen-Independent Prostate Cancer
Protocol: #0602008378
Title: Radioimmunotherapy Phase I Dose-Escalation Studies in Prostate Cancer using ^{177}Lu-J591 Antibody: Dose Fractionation Regimen
Protocol: #0810010067
Title: A Randomized Phase 2 Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) and Ketoconazole In Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy
Protocol: #0812010139
Title: ^{177}Lu-J591 Anti-Prostate Specific Membrane Antigen Monoclonal Antibody in Patients with Metastatic, Castrate Resistant Prostate Cancer.
Protocol: #0902010212
Title: ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591-GS (^{177}Lu-J591) in Patients with Nonprostate Metastatic Solid Tumors: A Pilot Study
Protocol: #100101851 – **PI, Douglas Scherr, MD**
Title: 111Indium-J591 Imaging of Localized Prostate Cancer

The Weill Cornell Medical College Data Safety Monitoring Board met on June 14, 2011 and reviewed the periodic reports for the above named protocols.

The WCMC DSMB carefully weighed the risks and benefits of these studies and noted that subjects have already failed between 1 and 4 chemotherapy regimens before starting these studies, have failed metacal and surgical castration, have metastatic prostate cancer and have a high mortality rate. Given that the minimum definition of efficacy is a 30% decline in PSA, and through the studies you have found 28% in the higher dose range are getting efficacy, the DSMB recommends that these trials continue with the following modification:

- Please submit your next DSMB report after the next 10 subjects have received the radioactive antibody, irrespective of which protocols they've been on. The reports must include grade of severity of each AE, as reported prior to May 8, 2009. Please amend all IRB protocols to reflect this monitoring provision.

If you have any questions, please contact us by emailing dsmb@med.cornell.edu or calling the DSMB Coordinator, Lauren Odynocki, at (646) 962-8192.

Thank you.

The Prostate Cancer Clinical Trials Consortium

June 24, 2011

Scott T. Tagawa, MD, MS
Medical Director, Genitourinary Oncology Research Program
Assistant Professor of Medicine & Urology
Weill Cornell Medical College
525 E. 68th Street, Box 403
New York, NY 10065

Dear Dr. Tagawa,

I am happy to write this letter in support of your study entitled "A Randomized Phase II Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) and Ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer after Local Therapy."

As you know, a proposal co-developed by Dr. Mark Stein of the University of Medicine and Dentistry of New Jersey and you was formally accepted for activation within the Prostate Cancer Clinical Trials Consortium (PCCTC) in April 2011. The study was presented to all PCCTC sites via teleconference on May 5, 2011 and discussed again at our group meeting in Chicago on June 2-3, 2011. Dr. Stein will serve as principal investigator and each site within the consortium now has the opportunity to open the study and receive PCCTC accrual credit.

Your external Department of Defense and Prostate Cancer Foundation funding makes the study of particular interest to our consortium. We look forward to collaborating.

Sincerely,

Jake Vinson
Director, Prostate Cancer Clinical Trials Consortium
Memorial Sloan-Kettering Cancer Center
Kimmel Center
353 East 68th Street, Room 431
New York, NY 10065
Ph. 646-422-4383
vinsonj@mskcc.org

cc: Dr. Mark Stein, Cancer Institute of New Jersey

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June 17, 2011

Scott T. Tagawa, MD
Assistant Professor of Medicine & Urology
Weill Cornell Medical College
525 E. 68th St., Starr 341
New York, NY 10065

Dear Scott,

I am pleased to provide this letter in further support of your DOD grant PC081664 entitled "A Randomized Phase 2 Trial of ^{177}Lu Radiolabeled Monoclonal Antibody HuJ591 (^{177}Lu-J591) and ketoconazole in Patients with High-Risk Castrate Biochemically Relapsed Prostate Cancer After Local Therapy".

As director of the WCMC Genitourinary Research Fund, I am willing to support the clinical trial with an additional $300,000 to support the cost of outside clinical sites. This will cover additional start up costs for each site, reimburse site personnel for time/effort in the conduct of the study, and pay for some correlative studies.

This clinical trial is an innovative and important study that may improve the lives of men affected by prostate cancer, the most common cancer in men. I look forward to these collaborative efforts.

Sincerely,

Neil H. Bander, M.D.
Bernard & Josephine Chaus Professor of Urological Oncology
Director, Laboratory of Urological Oncology